PATENT APPLICATION

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Alice C. MARTINO et al

For: TABLET FORMULATION

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Assistant Commissioner for Patents
Washington, DC 20231

**DECLARATION UNDER 37 CFR 1.132**

I, Alice C. Martino, declare:

THAT, I received a B.S. degree in Pharmacy from Purdue University in 1980;

THAT, I received a Ph.D. degree in Pharmaceutics from The University of Iowa in 1987;

THAT, I worked at G.D. Searle as an Industrial Pharmacist prior to graduate school from 1980 to 1982;

THAT, I worked at Burroughs Wellcome as a Pharmacy Intern in 1979;

THAT, I worked at Oquawka Professional Pharmacy as a Pharmacist from 1983 to 1986;

THAT, I worked at Walgreens as a Pharmacist and Pharmacy Intern from 1981 to 1982 and 1976 to 1977;

THAT, I worked at Keefer's Pharmacy as a Pharmacy Intern from 1976-1979;

THAT, I joined The Upjohn Company in 1987 as a Research Scientist;

THAT, I am the author or co-author of about nine external scientific publications, about three of which deal with delavirdine (RESCRIPTOR Tablet) formulation and product development;

THAT, I am the inventor or co-inventor of about nine U.S. Patent applications and one U.S. Patent;

THAT, my present position with Pfizer is Principal Research Scientist and my daily duties and responsibilities include design and execution of pharmaceutical formulation development from inception to product launch, including novel exploratory formulations, formulation advisor, leader of a formulation team, and leader of a pharmaceutical sciences project team;

THAT, being so qualified the declarant further states;

THAT, I am a co-inventor of the above-identified patent application.

MICROCRYSTALLINE CELLULOSE IS NOT A POLYMERIC BINDER AS THAT TERM IS USED IN THE ABOVE-IDENTIFIED APPLICATION

THAT, Microcrystalline cellulose (MCC) functions as a tablet diluent ands not truly a tablet binder. At least, not in the commonly used sense of the word, i.e., to bind together other key materials in the tablet especially the drug and other excipients which otherwise would not exhibit sufficient bond to form a manufacturable tablet. While it is true that MCC itself exhibits self-binding properties and can accommodate other excipients in this mix and yet form a manufacturable tablet, this is typically the case only if those excipients/drugs contain either a) another material already acting as binder itself or b) if those materials are sufficiently low enough in concentration such that properties of the MCC can override ie that an actual binder is not needed;

THAT, from the Handbook of Drug Excipients, 3rd Ed, 2000: under the delineated item #6 called Functional Category, the following descriptions are provided;

a) Povidone (PVP). Functional Category: Disintegrant, dissolution aid, suspending agent, **tablet binder**. p433

b) Hydroxypropylmethylcellulose (HPMC-cellulose ether): Functional Category: coating agent, filmformer, rate-

controlling polymer for sustained release, stabilizing agent, suspending agent, **tablet binder**, viscosity-increasing agent. p252

c) Hydroxypropylcellulose (HPC): Functional Category: Coating agent, emulsifying agent, stabilizing agent, suspending agent, **tablet binder**, thickening agent, viscosity-increasing agent. p 244

d) Microcrystalline cellulose (MCC): Functional Category: Adsorbent, suspending agent, **tablet and capsule diluent; tablet disintegrant.** p102

[notice that tablet binder is not listed under Functional Category here];

THAT, copies of the above referred to pages from the Handbook of Drug Excipients, 3rd Ed, 2000, are attached to and made a part of this Declaration;

THAT, while there are cases and references where loose terminology might cause someone to label MCC as a binder because it does increase tablet bond, the properties of the MCC material did not lend it to actually being listed in Functional Category as a tablet binder in this key common reference for the pharmaceutical industry. Microcrystalline cellulose does not get very sticky/adhesive nor provide film-former function when wetted, which a true binder does. In contrast, a regular binder not only increases tablet bond but more importantly and in addition when wetted provides a cohesive "glue" or film between materials which otherwise would not possess adequate adhesion or cohesion;

THAT, this same property of increasing adhesion or tackiness and film-formation when wetted of the polymeric binder defined in the above-identified application serves the function of delaying precipitation of the rapidly precipitating drug. The delay of precipitation provided by

MCC is inadequate for it to serve as a binder in the tablet composition defined in the above defined composition;

THAT, this inadequate delay of precipitation by MCC is borne out by the plot shown in Fig 1 which is attached;

THAT, Curve A shows the delay of precipitation profile of a soluble salt of a poorly soluble drug in the presence of hydroxy propyl methyl cellulose (HPMC);

THAT, Curve B shows the precipitation profile of a soluble salt of a poorly soluble drug in the absence of HPMC;

THAT, Curve C shows the precipitation profile of a soluble salt of a poorly soluble drug in the presence of MCC but no polymeric binder;

THAT, Curve C meets the definition of a rapidly precipitating drug as that term is defined in the above identified application (roughly 90% drug precipitates out of solution within 60 minutes to a less soluble form);

THAT, Curve C does not meet the requirement of delay of precipitation which is provided by the tablet composition claimed in the above identified application;

THAT, MCC is a separate and distinct component and is not a polymeric binder in the tablet composition or the above identified application.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 03 July 2003

Alice C. Martino

# Cellulose, Microcrystalline

## 1. Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcrystallinum
USP: Microcrystalline cellulose

## 2. Synonyms

*Avicel*; cellulose gel; crystalline cellulose; E460; *Emcocel*; *Fibrocel*; *Tabulose*; *Vivacel*.

## 3. Chemical Name and CAS Registry Number

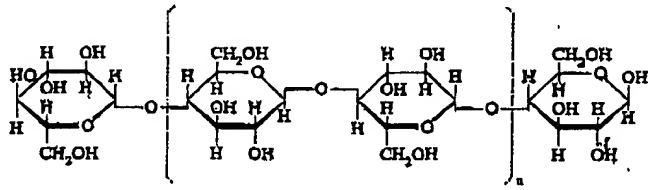
Cellulose [9004-34-6]

## 4. Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈ 36 000

Where n ≈ 220.

## 5. Structural Formula



## 6. Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

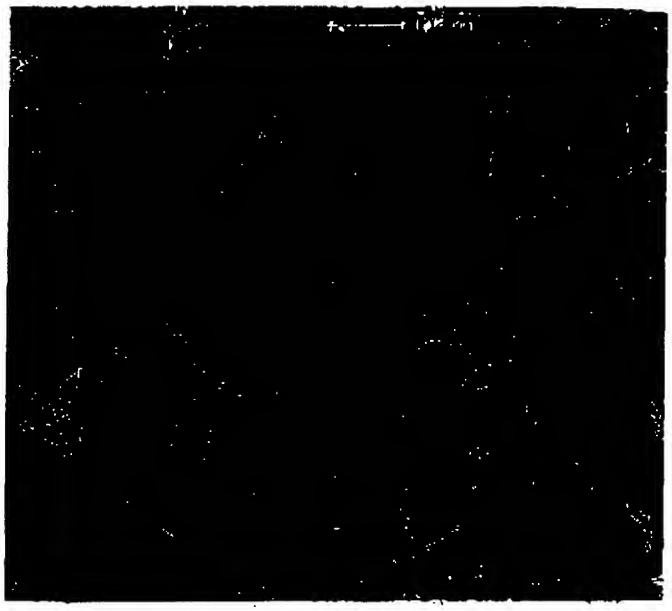
## 7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes.[1-7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products.

| Use | Concentration (%) |
|---|---|
| Adsorbent | 20-90 |
| Anti-adherent | 5-20 |
| Capsule binder/diluent | 20-90 |
| Tablet disintegrant | 5-15 |
| Tablet binder/diluent | 20-90 |

**SEM: 1**
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals
Lot: 98662
Magnification: 100×



## 8. Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades which have different properties and applications.

## 9. Pharmacopeial Specifications

| Test | JP | PhEur | USP |
|---|---|---|---|
| Identification | + | + | + |
| Characters | + | + | — |
| pH | 5.0-7.0 | 5.0-7.5 | 5.0-7.0 |
| Bulk density | + | – | + |
| Solubility | – | + | — |
| Loss on drying | ≤ 7.0% | ≤ 6.0% | ≤ 7.0% |
| Residue on ignition | ≤ 0.05% | – | ≤ 0.05% |
| Conductivity | + | – | + |
| Sulfated ash | – | ≤ 0.1% | — |
| Ether-soluble substances | ≤ 0.05% | ≤ 0.05% | ≤ 0.05% |
| Water-soluble substances | ≤ 0.24% | ≤ 0.25% | ≤ 0.24% |
| Heavy metals | ≤ 10 ppm | ≤ 10 ppm | ≤ 0.001% |
| Starch | — | + | — |
| Organic volatile impurities | — | — | + |
| Microbial limits | + | + | + |
| Assay | — | — | 97.0-102.0% |

# Hydroxypropyl Cellulose

## 1. Nonproprietary Names

BP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USP: Hydroxypropyl cellulose

## 2. Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

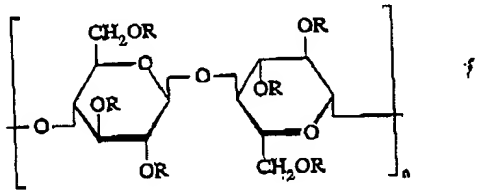
## 3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

## 4. Empirical Formula Molecular Weight

The USP describes hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or some other suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades which have different solution viscosities. Molecular weight ranges from 50 000-1 250 000, *see also* Section 10.

## 5. Structural Formula



Where R is H or $[-CH_2-CH(CH_3)-O]_mH$

## 6. Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

## 7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended release-matrix former. Concentrations of between 2-6% w/w of hydroxypropyl cellulose may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.[1-5] Concentrations of between 15-35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[6] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the hydroxypropyl cellulose viscosity and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Either aqueous solutions, containing hydroxypropyl cellulose along with some methylcellulose, or ethanolic solutions may be used.[7-9] Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant, *see* Hydroxypropyl Cellulose, Low Substitute.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.[10-12]

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

| Use | Concentration (%) |
|---|---|
| Extended release-matrix former | 15-35 |
| Tablet binder | 2-6 |
| Tablet film coating | 5 |

## 8. Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. *See also* Sections 4 and 5.

## 9. Pharmacopeial Specifications

| Test | PhEur | USP |
|---|---|---|
| Identification | + | + |
| Apparent viscosity | + | + |
| Appearance of solution | + | — |
| pH (1 in 100) | 5.0-8.5 | 5.0-8.0 |
| Loss on drying | ≤ 7.0% | ≤ 5.0% |
| Residue on ignition | — | ≤ 0.2% |
| Sulfated ash | ≤ 1.6% | — |
| Arsenic | — | ≤ 3 ppm |
| Chlorides | ≤ 0.5% | — |
| Lead | — | ≤ 0.001% |
| Heavy metals | ≤ 20 ppm | 20 ppm |
| Silica | ≤ 0.6% | — |
| Organic volatile impurities | — | + |
| Assay of hydroxypropoxy groups | — | ≤ 80.5% |

## 10. Typical Properties

*Acidity/alkalinity*:
pH = 5.0-8.5 for a 1% w/v aqueous solution.

*Density (bulk)*: = 0.5 g/cm$^3$

*Interfacial tension*: 12.5 mN/m for a 0.1% w/v aqueous solution vs. mineral oil.

*Melting point*: softens at 130°C; chars at 260-275°C.

*Moisture content*: hydroxypropyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content, and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are: 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity. *See* Table I. *See also* Figs. 1, 2, and 3.

# Hydroxypropyl Methylcellulose

## 1. Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

## 2. Synonyms

*Benecel MHPC*; Cellulose, hydroxypropyl methyl ether; E464; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*.

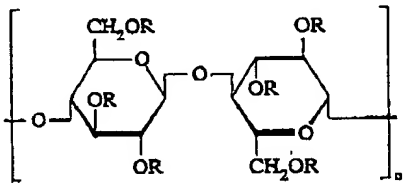
## 3. Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether [9004-65-3]

## 4. Empirical Formula Molecular Weight

The PhEur describes hydroxypropyl methylcellulose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hydroxypropyl methylcellulose defined in the USP specifies the substitution type by appending a four digit number to the nonproprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group ($OCH_3$). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000.

## 5. Structural Formula




Where R is H, $CH_3$, or $[CH_2CH(OH)CH_2]$.

## 6. Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

## 7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder,[1] in film-coating,[2–7] and as an extended-release tablet matrix.[8–12] Concentrations of between 2–5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations between 2–20% w/w are used as film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hydroxypropyl methylcellulose is used in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

## 8. Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

## 9. Pharmacopeial Specifications

| Test | JP | PhEur | USP |
|---|---|---|---|
| Identification | + | + | + |
| Appearance of solution | + | + | — |
| pH (1% w/w solution) | 5.0–8.0 | 5.5–8.0 | — |
| Apparent viscosity | + | + | + |
| Loss on drying | ≤ 5.0% | ≤ 10.0% | ≤ 5.0% |
| Residue on ignition | | | |
| For viscosity grade > 50 mPa s | ≤ 1.5% | — | ≤ 1.5% |
| For viscosity grade ≤ 50 mPa s | ≤ 1.5% | — | ≤ 3.0% |
| For type 1828 of all viscosities | ≤ 1.5% | — | ≤ 5.0% |
| Sulfated ash | — | ≤ 1.0% | — |
| Chlorides | — | ≤ 0.5% | — |
| Heavy metals | — | ≤ 20 ppm | ≤ 0.001% |
| Methoxy content | | | |
| Type 1828 | — | — | 16.5–20.0% |
| Type 2208 | 19.0–24.0% | — | 19.0–24.0% |
| Type 2906 | 27.0–30.0% | — | 27.0–30.0% |
| Type 2910 | 28.0–30.0% | — | 28.0–30.0% |
| Hydroxypropoxy content | | | |
| Type 1828 | — | — | 23.0–32.0% |
| Type 2208 | 4.0–12.0% | — | 4.0–12.0% |
| Type 2906 | 4.0–7.5% | — | 4.0–7.5% |
| Type 2910 | 7.0–12.0% | — | 7.0–12.0% |

# Povidone

## 1. Nonproprietary Names

JP: Povidone
P: Povidone
PhEur: Polyvidonum
USP: Povidone

## 2. Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

## 3. Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

## 4. Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ 2500-3 000 000

The USP describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. The K-value is calculated using Fikentscher's equation[1] shown below:

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the K-value × $10^{-3}$, and c is the concentration in % w/v.

Alternatively, the K-value may be determined from the following equation:

$$\text{K-value} = \sqrt{\frac{300c\log z+(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

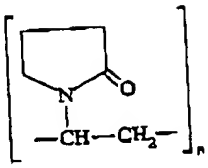
where z is the relative viscosity of the solution of concentration c, k is the K-value × $10^{-3}$, and c is the concentration in % w/v.

Approximate molecular weights for different povidone grades are shown below:

| K-value | Approximate molecular weight |
|---|---|
| 12 | 2500 |
| 15 | 8000 |
| 17 | 10 000 |
| 25 | 30 000 |
| 30 | 50 000 |
| 60 | 400 000 |
| 90 | 1 000 000 |
| 120 | 3 000 000 |

*See also* Section 8.

## 5. Structural Formula



## 6. Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

## 7. Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a disintegrant [4,5] and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[6-8] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations, *see* Section 14.

| Use | Concentration (%) |
|---|---|
| Carrier for drugs | 10-25 |
| Dispersing agent | Up to 5 |
| Eye drops | 2-10 |
| Suspending agent | Up to 5 |
| Tablet binder, tablet diluent, or coating agent | 0.5-5 |

## 8. Description

Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and exist as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and exist as plates.

## 9. Pharmacopeial Specifications

| Test | JP | PhEur | USP |
|---|---|---|---|
| Identification | — | + | + |
| Characters | + | + | — |
| pH | — | — | 3.0-7.0 |
| K ≤ 30 | 3.0-5.0 | 3.0-5.0 | — |
| K > 30 | 4.0-7.0 | 4.0-7.0 | — |
| Appearance of solution | + | + | — |
| Water | ≤ 5.0% | ≤ 5.0% | ≤ 5.0% |
| Residue on ignition | ≤ 0.1% | — | ≤ 0.1% |
| Sulfated ash | — | ≤ 0.1% | — |
| Lead | — | — | ≤ 10 ppm |

## Typical Concentration vs Time Profile

**(Graphs Based on Data from Delavirdine Development)**